Remediation of depression-related cognitive impairment:

Cognitive Control Training as treatment augmentation

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Abstract

Introduction: Despite several available evidence-based interventions for major depression relapse rates remain high and relapse prevention programs are still scarce. In order to increase effectiveness, novel techniques that target underlying vulnerability factors may be a promising avenue. Depression is associated with impairments in executive functioning, which is in turn associated with poor psychosocial outcomes and more Repetitive Negative Thinking (RNT), a key vulnerability factor for relapse. In this paper, we examine deficits in cognitive control as a potentially modifiable causal mechanism for depression.

Areas covered: An overview of studies on the interplay between cognitive control and RNT is presented, assessing the potential of training cognitive control in depressed individuals. Cognitive Control Training (CCT), or other techniques aimed at remediating executive functioning, provide an interesting way to examine the causal status of executive functions in depression-related symptoms, such as emotion regulation and psychosocial functioning. We also assess the clinical utility of CCT.

Expert commentary: There is emerging evidence for clinical utility of CCT but more large-scale, longitudinal studies are required. We discuss how the adaptive PASAT can be used as a technique that can be combined with psychological as well as biological interventions, to increase overall effectiveness of treatment for depression.

Keywords: Cognitive Control, Cognitive Control Training, Depression, Executive Functioning, Remediation, Repetitive Negative Thinking, Treatment Augmentation

1. Introduction

Although there are currently several evidence-based interventions for major depression, effects are still unsatisfactory, as a considerable amount of individuals do not respond to available first line treatments [1]. Moreover, the risk for recurrence of depressive episodes after remission remains high [2, 3] and increases further with each episode [4]. These findings indicate that key vulnerability mechanisms are not sufficiently addressed in current treatment approaches [5]. Repetitive Negative Thinking (RNT: [6]), typically measured using standardized self-report questionnaires, is an important vulnerability factor within and beyond the context of depression [7-10]. Several researchers suggest that difficulties interrupting RNT and deploying alternative emotion regulation strategies (e.g., reappraisal and problem solving) are related to deficits at the level of cognitive control [11, 12]. Interventions that directly target cognitive control might enhance the effectiveness of both psychological and biological (i.e., pharmacological and neuro-stimulation) interventions for depression [13, 14].

2. Cognitive Control Training for Depression

Cognitive control can be defined as the ability to flexibly adapt thoughts and behavior as a function of one's goals, and is often used synonymous to Executive Function (e.g., [15, 16]). Theoretical accounts specify that exerting cognitive control is related to various cognitive functions (e.g., selective attention, working memory, inhibitory control, task switching), necessary to reach these goals (e.g., [17-19]). Researchers frequently fractionate cognitive control into various subcomponents including Shifting (between mental sets), Updating (of working memory contents), and Inhibition (of prepotent responses) [20]. Although this three-component framework has several limitations [21], it allows for more precise definitions of key processes involved in cognitive control. Indeed, impaired cognitive control has been observed

in depressed individuals, using different cognitive neuropsychological tasks [22-25]. Here it is noteworthy that these impairments have been established at the group level, so do not necessarily apply to all depressed individuals. Moreover, there is ongoing debate to what extend these impairments are due to motivational influences, causing worse cognitive performance [21, 26, 27].

Interestingly, impairments in cognitive control also persist during remission (e.g., [28]), with more episodes being associated with more severe deficits [29]. Rather than cognitive control deficits being a by-product of depression, there is emerging evidence suggesting a causal role of cognitive control, as cognitive control is required to disengage from negative thoughts [12] and to implement more adaptive strategies [30], such as reappraisal [31]. Cognitive control deficits have been demonstrated in undergraduates reporting high levels of RNT [32, 33], with recent meta-analytic data (n = 6698, including unselected, screened and clinical samples) suggesting that specifically the discarding of no longer relevant information from working memory is related to RNT [34]. It has also been shown that RNT mediates the relationship between impaired cognitive control and residual symptoms in remitted depressed individuals [35]. In addition, cognitive control is predictive for RNT following a stressful event in healthy convenience samples [36]. Conversely, stress has a negative impact on cognitive control, with a stress-induced decrease of cognitive control predicting depressive symptoms prospectively in an unselected sample of undergraduates [37]. Importantly, deficits in executive functioning are related to occupational impairment (e.g., work loss) in depression [38], even in a remitted stage [39]. Data from 3703 depressed individuals suggests that experiencing concentration difficulties and indecisiveness explains a high amount of unique variance in self-reported overall impairment (encompassing work, home management, social activities, private activities and close relationships), that is comparable to loss of interest, fatigue and sad mood [40].

Despite the crucial role of cognitive impairment in depression, it is not yet considered as a specific target of treatment [41]. Techniques that specifically seek to improve executive functioning/cognitive control are not part of current psychotherapy programs for depression, even though specific cognitive remediation programs exist [42]. In addition, existing treatments for depression show limited effects in terms of modifying cognitive vulnerability factors. For instance, RNT is a common residual symptom following remission of depression [43] and so are cognitive problems [44]. Similarly, results from a recent clinical trial suggest that the effects of pharmacotherapy on cognitive impairment are limited as well [45]. Although some studies suggest that various antidepressants may have beneficial effects on cognitive function in depression [46, 47], it has been shown that performance after 24 weeks of SNRI or SSRI treatment is still significantly worse as compared to healthy controls [48]. Overall, the prevalence of (residual) cognitive deficits [44], in spite of treatment, indicates that currently available antidepressants are insufficient to fully remediate cognitive control problems [49]. New multi-modal compounds (i.e., products having more than one therapeutic action) hold potential for treating major depressive disorder [50], including the cognitive dysfunctions [49]. Regardless of the potential of multi-modal antidepressants, there is a pressing need for strategies directly targeting cognitive function, as some impairments (e.g., sustained and selective attention, memory and executive function) seem resistant to current treatments [51]. In this context, Cognitive Control Training (CCT) shows great potential as an add-on or preventive intervention [13, 14].

CCT refers to the repeated use of computerized tasks that target executive functions. Various procedures have already been developed to operationalize CCT, such as the adaptive Paced Auditory Serial Addition Test (aPASAT: [52]), Flanker Tasks (e.g., [53]) or Dual n-back tasks (e.g., [54] and [55]). A recent meta-analysis suggests that cognitive training has therapeutic potential in the context of depression, with small to moderate effects on symptom

severity, daily functioning, attention, working memory and global functioning [56]. These effects are hypothesized to be at least partly mediated by effects of CCT on RNT [57]. To illustrate this pathway, the procedure of the aPASAT will be discussed, given that this is one of the most widely used CCT procedures.

In the PASAT [58] participants are presented an auditory stream of digits (between one and nine), and a visual array of numbers (from one to eighteen). Participants have to continuously add up the last two heard digits and click or tap on the corresponding sum. In the *adaptive* version of the task, the inter-trial interval (ITI) changes depending on the participant's performance [52]. The pace of the auditory stream of digits will gradually increase for participants performing well on the task. Similarly, consecutive incorrect responses (including non-responses) result in a slightly decreased pace. By design, participants are confronted with decreasing ITI's and a high occurrence of incorrect responses, often instilling frustration during the task. For the purpose of training, this task is conducted multiple times (e.g., ten 15-minute sessions over the course of two weeks). During the task, participants have to put effort into sustaining their attention. Furthermore, at the level of working memory, participants need to keep track of the most recent pair of digits and add them up, while avoiding interference from previous responses. In addition, the high occurrence of task-related errors due to the decreasing ITI is to some extent a stressful experience which may trigger RNT while performing the aPASAT. This further increases the cognitive load [59] in a naturalistic way, potentially facilitating the transfer of exerted cognitive control to RNT upon confrontation with naturalistic stressors.

Theoretically, the task demands of the aPASAT correspond with the Attention Control mechanism of working memory: the ability to select goal-relevant information and responses, while resisting distraction [60]. In terms of the three-component model [20], Updating forms a central feature of the aPASAT: there is a constant revision of the stimuli (i.e., relevant digits)

kept in working memory, where interference may occur from task-irrelevant information (e.g., the previous sum, RNT). As such, performance on the aPASAT also reflects interference control, among which the ability to inhibit intrusive thoughts [61] or to discard such thoughts from working memory [34]. The task can thus also provide learning experiences for avoidant participants by exposing them to negative thoughts and the physiological experience of stress, in addition to or instead of remediating the cognitive processes described above. More research into these training mechanisms is needed to conclude whether either or both hypotheses are correct.

Several alternatives to the aPASAT have been proposed, targeting similar executive processes. For instance, during the dual N-back task, participants have to simultaneously keep track of two separate streams of information (e.g., location of a square in a grid and the identity of an orally presented letter [54]) and indicate whenever there is a match in either stream between the current stimulus and the stimulus n trials back. In the Flanker Task [62] on the other hand, participants are asked to indicate the orientation of a target arrow as quickly and as accurately as possible, which requires response inhibition in trials with distractor arrows pointing in the opposite direction.

Research on CCT in undergraduates reporting high levels of RNT suggests that ten sessions of the aPASAT (as compared to an active control condition) can buffer against RNT, both in response to stressors in highly controlled lab situations [63] and in response to naturalistic stressors [63, 64]. In addition, more intensive CCT procedures using an emotional variant of the N-back task (20 daily 20- to 30-minute sessions) in an unselected sample of undergraduates have shown to result in improved downregulation of emotional distress, coupled with increased activity in brain regions involved in emotion regulation [55]. Moreover, recent findings in healthy participants suggest that performing three 15-minute sessions of a modified Flanker task per day over the course of six consecutive days can impact amygdala

reactivity (a subcortical region related to emotional processes), presumably by stimulating connectivity with frontal areas, to downregulate amygdala activity [65]. These neural indicators are in line with the notion of improved cognitive control over emotional information. This implies that targeting cognitive deficits may be important, as improvements in cognitive functioning are also likely to positively impact mood and other depressive risk factors. Although the evidence is not yet fully conclusive, including some studies that did not find beneficial effects of CCT [66-68], there seems considerable evidence for therapeutic potential of CCT [69]. A recent systematic review of the literature on CCT in at-risk, depressed and remitted depressed samples, which also includes proposed explanations for null findings (e.g., a training protocol that is not sufficiently intensive, participants that are not engaged with the training, inclusion of participants without clear deficits), can be found elsewhere [70].

3. Conclusion

To summarize, cognitive deficits are common and major complaints in the context of depression [25, 38], and are an important risk factor for the recurrence of depressive episodes. However, these processes are not sufficiently targeted by existing interventions. The core idea of CCT is to stimulate efficient use of working memory and attentional processes, by repeatedly practicing these cognitive functions in a challenging task-context. In CCT procedures where task difficulty increases, participants are encouraged to exercise cognitive control to successfully perform the training task, which entails down-regulating task-irrelevant thoughts or feelings. Given that these processes are trained in an affective, stressful task-context, beneficial effects of CCT on cognitive functioning might transfer to stressful situations, allowing participants to exert control over emotion regulation processes (e.g., inhibiting RNT). Due to this interplay between cognitive control and emotion regulation, augmenting other therapeutic interventions with CCT seems a promising and interesting venue for future research.

4. Expert Commentary

CCT *by itself* will likely not suffice as an intervention for the majority of depressed individuals. However, CCT is expected to be a valuable additional active ingredient, potentially augmenting the effectiveness of existing treatments. In the following paragraphs, the merit of supplementary CCT will be outlined for psychotherapy in general, as well as for Rumination-Focused Cognitive-Behavioral Therapy (RFCBT: [71, 72]) and Mindfulness [73] in particular. Lastly, the role of CCT in neurocognitive interventions is briefly introduced, as yet another opportunity for further research into the clinical use of CCT.

The augmentation of psychotherapy is of special interest, as various programs provide a broader framework in which CCT can be embedded. Supplementary aPASAT sessions, in the form of an extra homework assignment for instance, may provide a larger window of opportunity for alternative emotion regulation strategies, that are often an explicit focus in psychotherapy, but do not necessarily improve through CCT alone [64]. In other words: investing in alternative emotion regulation strategies is particularly worthwhile when individuals are more able to put these strategies to use, which requires a certain level of control over RNT to begin with. Only improving cognitive control over RNT, through computerized training, may not be sufficient either: without alternative strategies to replace RNT, one could be easily pulled back into the next loop of negative thoughts. Moreover, individuals with positive metacognitions regarding RNT (e.g., viewing RNT as a useful strategy to reach a solution or achieve insight) may mobilize cognitive control to intentionally engage in RNT. As such, practicing alternative emotion regulation strategies and/or simultaneously targeting metacognitions about RNT [74, 75] might be necessary.

In addition, CCT and more traditional psychotherapeutic interventions can complement one another. For instance, tasks like the aPASAT can function as a behavioral experiment, providing key insights about stress and emotion regulation that can enrich the clinical process. Simultaneously, clinicians can play a crucial role in motivating their patients for CCT. The importance of a strong rationale that is convincingly communicated is not to be underestimated, given that task engagement predicts the effectiveness of CCT [76].

The above considerations suggest that CCT can have merit for psychotherapy in general. In our opinion however, future research and implementation efforts should primarily focus on therapeutic frameworks that provide the best mechanistic fit with CCT, as this likely has the most potential for synergetic effects. RFCBT [71, 72] is an example of such a framework. The core interventions in RFCBT include recognizing warning signs for RNT, in order to respond differently, in one of two ways. The patient can either replace unproductive loops of negative thoughts [77] with alternative behavior (e.g., asking for feedback, rather than dwelling on the impression he/she *might* have made during a presentation), or the patient can defuse RNT by shifting away from its abstract, general and evaluative style [78, 79]. Both the replacement of RNT with alternative behavior and the shifting away from RNT to more constructive thoughts, requires cognitive control. Especially when RNT has become a mental habit, its continuous interruption can be difficult, which in turn hinders attempts to respond differently. This is where CCT could improve the disengagement from RNT, allowing more room for the implementation of alternative responding.

Mindfulness is another intervention that is consistent with CCT from a mechanistic point of view. Similar to CCT, mindfulness relates to attention control: dismissing elaborative processing (such as RNT) to regain focus. In the context of CCT, the individual has to pay attention to the task at hand (e.g., the numbers presented in the aPASAT). Mindfulness, by contrast, requires individuals to foster awareness of thoughts, feelings and sensations [73].

Crucially, individuals have to approach these psychological and physiological events in a curious and open-minded manner: observing the flow of experiences, without getting caught up in judgmental thinking [73]. This accepting attitude is not encouraged in CCT, where there is an orientation towards performance. In our opinion, integrating a stance of performance as well as a stance of acceptance in treatments for depression is key, so that individuals learn to flexibly take either or both of these stances in daily life, depending on the context [80]. Other advantages of adding CCT relate to its frustrating and more guided nature (due to immediate feedback in the task). The former allows individuals to practice attention control under stress. The latter may be valuable when individuals, for whatever reason, find it difficult to use mindfulness.

Finally, CCT can also augment non-psychological interventions, given that tasks such as the aPASAT can be combined well with biological techniques that are used to directly counter dysregulated recruitment of prefrontal brain areas in depression [81]. Unfortunately, pharmacotherapy and methods such as Repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS) alone do not suffice to achieve stable normalization of prefrontal activity and cognition in depression, suggesting that individuals may require new learning in order to prolong the short-term effects of neuro-stimulation [82]. The immediate effects of neuro-stimulation can set the stage for CCT, providing individuals the opportunity to carry out CCT sessions, allowing them to practice specific executive functions [83]. An in-depth overview of such a neurocognitive intervention falls outside of the scope of this paper, but can be found elsewhere [82, 83].

More research outside the lab is needed to further build the evidence base of CCT in general and as an augmentation for existing interventions for depression in particular. By targeting cognitive deficits and the bouts of RNT that are fueled by such deficits, overall effectiveness of existing treatment programs may improve [84]. The interplay with alternative emotion regulation strategies, the impact of metacognitions, and the necessity of a strong

rationale to increase task engagement potentially explain some null findings in the literature, while also emphasizing the possible importance of combining CCT and psychotherapy as a promising way forward. Recently, researchers started adding CCT to psychotherapeutic interventions, with varying degrees of success. In a study comparing CCT, mindfulness, their combination and a control group (i.e., a placebo version of the CCT), it was found that *only* participants in the combined group showed a continued reduction in self-reported RNT one week after the intervention [85]. However: this finding might simply be the result of receiving a higher total dose of psychotherapy in the combined condition. In another study, CCT did *not* seem to increase the effect of behavioral activation [86], perhaps due to the augmentation of an already highly effective intervention with a limited amount of CCT sessions. Both studies also suffer from small sample sizes as well as limited follow-up, which constrain the clinical implications that can be drawn.

5. Five-year view

If RCTs further confirm the efficacy of CCT, it is likely that in five years clinicians will be able to incorporate CCT in their practice, by providing individuals suffering from depression with psycho-education as well as online tools necessary for training. The aPASAT has a simple design that could readily be moved outside of the lab. Research teams investigating CCT and similar computerized interventions need to be willing to invest time and funding into the dissemination of promising techniques, in order to increase uptake by both clinicians and their patients. This requires translational work from lab studies to larger scale dissemination studies where the input of stakeholders and users is a key requirement [87].

Despite the fact that cognitive problems are frequent in depression and can be debilitating, it is unlikely that cognitive impairments are a major problem for all depressed individuals. Hence,

we argue that CCT should be offered to patients that, based on their individual case formulation, are expected to profit from the technique. From a practical point of view, this means that a standardized diagnostic version of the task may be informative to examine whether CCT is needed. Taking this a step further, the clinician could even use the task performance and the individual's experiences (e.g., stress and repetitive negative thoughts) during the first few sessions as input for a person-specific dynamic assessment, together with symptom fluctuations [88]. Moving towards such individualized assessment and targeted intervention seems a most promising way forward.

Key Issues

- Effects of interventions for depression are unsatisfactory, as a considerable amount of individuals do not respond to first line treatments. New techniques that help targeting underlying vulnerability processes, such as Repetitive Negative Thinking, are therefore necessary.

- The extent to which individuals are able to fend off Repetitive Negative Thinking, particularly when under stress, is related to one's cognitive control. People suffering from depression often show cognitive control deficits, hindering disengagement from negative thoughts. Cognitive Control Training has therefore potential as add-on technique.

- Supplementary Cognitive Control Training can fill an important gap in the current therapeutic arsenal for depression, as existing psycho- and pharmacological treatments do not fully remediate the cognitive deficits found in depression, even following remission.

- The results of studies on the effects of Cognitive Control Training are promising, given that it has been repeatedly shown to buffer against Repetitive Negative Thinking in response to stress. In addition, a recent study also points at increased activity in brain regions associated with emotion regulation, coupled with improved down-regulation of emotional distress.

- Cognitive Control Training might open up a bigger window of opportunity for alternative emotion regulation strategies, that are often an explicit focus of treatments, but do not necessarily improve through CCT alone. When considering Cognitive Control Training as a treatment augmentation, it is important to embed the training in existing frameworks, that also provide a good mechanistic fit.

- Psychological treatments such as Rumination-Focused CBT or Mindfulness, as well as neuro-stimulation may benefit from being combined with Cognitive Control Training.

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